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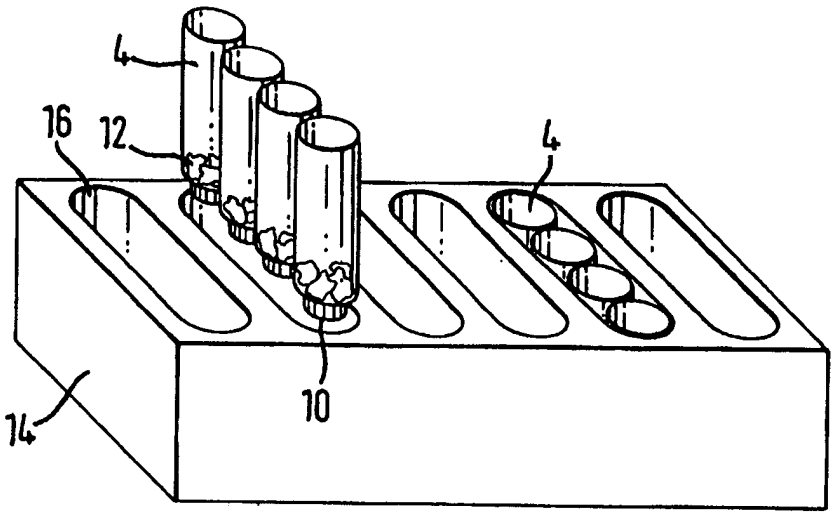

(57) Abstract

A method for solid phase synthesis, wherein a resin (12), having a first compound bonded thereto is deposited in a first container (4), the container having a porous base (10). The first container (4) is placed in a second container (16) having a solution of a second compound therein, such that the solution permeates through the porous base (10) and the second compound is allowed to react with the first compound to produce a product bonded to the resin (12). The first container is removed from the second container and is positioned above a third container. A cleaving solution is washed through the first container to thereby cleave the product from the resin, and the product is collected in the third container.

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REACTION APPARATUS FOR SOLID PHASE SYNTHESIS AND METHOD OF USING THE SAME

The present invention relates to an apparatus for performing chemical reactions and a method of using such apparatus.

It is known in the synthesis of chemical compounds for reactions to be carried out on a batch basis using a reaction tray. A reaction tray comprises a block of discrete wells arranged in a regular, usually rectangular, configuration, each well having a sufficient volume to accommodate the reagents for a particular reaction. Such trays are particularly useful in batch processes, as the wells are accurately fixed in their respective positions and thus a robot can be used to repeatably carry out steps of a reaction process, such as dispensing reagents. Furthermore, whole rows or columns of the tray can be acted on in a single step, for example by using a multi-pipette. Thus, the use of such trays provides an increase in efficiency during chemical processes such as synthesis by allowing batch processing.

One type of reaction in which the above trays may be used is solid-phase synthesis. In such a scheme granules of a resin, or other solid material suitable for use as a substrate, having suitable surface reaction sites are deposited in one or more wells of a tray. A first reagent is bound to the surface reaction sites. Such resins are widely available for such a process and may even be purchased with a desired base reagent bound to the reaction surface.

In such a known reaction process, a solution of a second reagent is deposited in each of the wells and this second reagent reacts with the reagent bound to the resin to form a desired product, which will itself be bound to the resin. The resin granules are then removed

from the wells of the tray using a pipette and are deposited in corresponding wells of a further filtration tray similar to that described in EP-A-0454315. Each well of the filtration tray is frusto-conical and open at its lower end. Across this lower opening inside each well is positioned a filter of nylon frit. The filtration tray is located over a further collection tray having a corresponding number of wells and the resin granules are washed to remove any remaining second reagent. The product is separated from the substrate by subsequent washing with a cleaving solution, usually an acid solution, to cleave the product from the resin surface.

This known method represents an increase in efficiency over earlier methods which do not utilise reaction trays, as the granules may be deposited in their initial wells by a robot. Additionally the solution of reagent compound may also be applied by a robot. However, the removal of the granules and solution from the wells cannot currently be achieved robotically, as a robot cannot ensure that the entire content of a particular well has been removed. Thus this represents a time consuming step requiring human intervention which considerably slows the synthesis process.

According to one aspect of the present invention there is provided a method for solid phase synthesis, wherein there is provided a first container having deposited therein a solid phase substrate to which is bonded a first reagent, the first container having a porous base; the first container is placed in a second container; a solution of a second reagent in the second container is permitted to permeate through the porous base of the first container; the second reagent is allowed to react with the first reagent to produce a product bonded to the substrate; the first container is removed from the second container; and a cleaving

solution is washed through the first container to cleave the product from the resin, the cleaving solution and the cleaved product being collected in a third container.

The present invention, therefore, has the advantage that the reaction between the two reagents at the surfaces of the substrate and the washing of the substrate with the cleaving solution take place in a single container. In this way, the need to remove the substrate from a reaction container to a wash-through container using a pipette is obviated. This results in a considerable saving in time and labour, particularly during batch synthesis processes. Thus, by means of the invention, less of the reaction process must be carried out by hand, and more automation of the process is possible.

The substrate may be in the form of granules of a resin, as is known in the art. The first reagent may be added to the substrate whilst in the first container, or the substrate may be treated with the first reagent prior to being placed in the first container. The second reagent may be placed in the second container prior to the first container being received, or may be added after the first container has been received by the second container.

In general, the substrate will be washed once the product has been formed to remove the excess second reagent. This additional washing step may take place either before or after the first container is removed from the second container. For example, the second container may be provided with an outlet in its base to allow the egress of the second reagent therefrom. In this case, the second reagent may be allowed to flow out from the second container, before a suitable washing solution is applied to the substrate, which solution may also be allowed to flow from the second container through the outlets. Alternatively or additionally, the

first container may be removed from the second container before a washing solution is allowed to pass over the substrate.

In normal use the method will involve the simultaneous treatment of a plurality of first containers, with corresponding second containers and third containers. One second container may receive a plurality of first containers, for example if each first container has a different first reagent which are to be treated with the same second reagent. In general a separate third container will be provided for each first container, so that the products are kept distinct.

The first containers may be separate physical items such as individual tubes, or may be groups of containers, such as a row to be received in an elongate second container.

The first container is preferably in a form such that it may be used with a standard reaction tray as described above. Such a form allows the first container to be aligned for deposition of the substrate by a robot, and the subsequent steps of the process may be similarly automated. Generally, the synthesis process will utilise a batch technique so that a number of, possibly different, synthesis reactions can be carried out simultaneously. For example, using a reaction tray arrangement having 96 wells configured as 12 columns of 8 wells, each column may be assigned a different second reagent solution and each row may be assigned a different first reagent bonded to the substrate. Thus, in this example 96 different reactions can take place on one tray. Of course, the particular numbers of rows and columns are arbitrary, as is the configuration of the wells which need not be rectangular but could be, for example, circular.

A particularly convenient design for the first container is in the form of a tube. The tube may be of any suitable cross-section, for example, square,

rectangular or elliptical, although in the preferred embodiment a circular cross-section is used. The cross-section of the tube need not be constant along its length, for example the tube may be flared at its upper end to aid dispensing of the substrate or reagents and/or may be flared at its lower end to increase the area of the porous base. This tube may have a rebated portion at its lower end to allow the tube to be push fit into a corresponding hole in a reaction tray. The reaction tray in this case is merely a convenient means for aligning the tubes in a regular arrangement for batch processing, and thus any suitable support means would be equally appropriate.

The first container may be, for example, of moulded plastics and for ease of handling a number of first containers may be connected to form a block, for example, corresponding to one row or column of a reaction tray array. In the case of connected tubes, the recessed portions of the connected tubes may be separately formed to facilitate the above described push fit. Tubes of this type are commercially available as extenders for reaction trays to increase the volume of the wells, for example during filtration.

The porous base of the first container may be a frit of, for example, nylon or microporous PTFE. The base may be in the form of a plug which may be frictionally retained in a lower open end of a first container such as the above-described tube. Alternatively, such plugs may be retained on an internal shoulder of the tube, for example one formed by the moulding of the recessed portion.

A plurality of second containers may be provided which will preferably be grouped in a regular arrangement. For example, each second container may be adapted to receive a plurality of first containers or an individual first container.

In one embodiment, the second containers are in the

form of a number of blind holes formed in a block and corresponding in arrangement to the wells of a reaction tray. The holes may be arranged to each accept one first container, such as the tubes described above. In this case, each of the holes would contain a second reagent, which may be a different reagent for each hole. Alternatively, the holes may be of a size and shape to receive a plurality of first containers. For example, in the case of grouped first containers, such as the joined tubes described above, the holes may be elongate to accommodate a whole row of tubes. Of course, in this case each elongate hole will contain a single second reagent, but each of the tubes may contain a substrate with a different first reagent bonded thereto as the reaction takes place at the substrate surface and there will therefore be no product cross-contamination, via the second reagent, between the tubes.

From a further aspect therefore, the present invention provides a method for solid phase synthesis comprising the steps of:

providing a plurality of reaction tubes, each reaction tube being provided at its lower end with a porous filter, and containing a solid-phase substrate having a first reagent bonded to a surface therefore, the reaction tubes being joined into a plurality of groups, each group comprising a plurality of tubes;

providing a reaction block having formed therein a plurality of reaction wells, each dimensioned to receive one of said groups of reaction tubes and each containing a second reagent in fluid form; and

locating the groups of reaction tubes in respective reaction wells such that the second reagent permeates through the porous filter of each reaction tube and reacts with the first reagent bonded to the solid-phase substrate in each reaction tube to form a product bonded to the solid-phase substrate.

Thus, according to this method a single reaction

well receives a plurality of reaction tubes whereby a single second reagent may be used to treat a plurality of different first reagents. This arrangement is particularly advantageous in the preparation of large lead discovery libraries.

Preferably, the second container or group of second containers (reaction block) is provided with a removable lid which may be attached once the first container(s) (reaction tubes) has/have been placed in the second container(s). The second container(s) or lid may be provided with a seal or seals, for example of rubber, to prevent leakage from the second container(s) when the lid is in place and during subsequent handling. Such seals may be arranged to prevent cross-contamination between adjacent second containers when the group of second containers is moved or agitated. The seals may be arranged to be captured between the upper edge(s) of the second container(s) and a lid, when the lid is fastened in place. The material selected for the seal may be varied so that it is compatible with the reagents used for any particular reaction. The lid is an optional feature of the reaction system according to the invention, which may be used to contain volatile reagents or to isolate the reagents from the external atmosphere. Advantageously, the second container and/or the lid thereof may be provided with inlets so that the internal volume of the second container may be filled with suitable gases to maintain an inert atmosphere.

The second container or group of second containers may be made of, for example, PTFE or stainless steel and may be manufactured by, for example, machining, moulding or casting.

During synthesis processes it is often required for the reagents to be heated or cooled to specific temperatures, for example in the range of -50°C to 120°C. Advantageously, therefore, the internal and/or external walls of the second container(s) may have formed therein

heat conduction passages for the passage of a coolant or heating medium, or alternatively the walls may have heating elements set therein or attached thereto for connection to an external heat source such as an electrical supply. Microwave heating may also be used to heat the contents of the second container.

The first container will generally fit into the second container flush with, or slightly below, the upper edge of the second container, so that a lid can be fitted thereto. In the case of the first containers projecting from the second containers, recesses may be provided in the lid to accommodate such projection, which advantageously aids the automatic removal of the first containers from the second container by a robot. A sufficient air space must be provided above the surface of the second reagent in each second container to facilitate permeation of the second reagent into the first container. If the first containers are arranged to be flush with the upper edge of the second container, means may be provided to aid removal of the first containers from the second container. For example, a cap may be provided which engages in an upper opening of the first container. Such a cap may push fit into the upper end of the first container and the resultant friction fit will be sufficient to allow the first container to be pulled out of the second container using the cap. This is of particular advantage when the first container(s) are individually located in respective second containers. The cap or removing means may be arranged in the form of a plurality of caps or removing means, for example corresponding to one grouping of first containers, such as one row of a reaction tray array, so that a number of first containers may be removed in one operation.

Viewed from another aspect, the invention provides apparatus for carrying out solid phase synthesis comprising a plurality of first containers which are

tubular, have openings at either end and are provided with a porous plug at one end; a plurality of second containers grouped together and adapted to receive the first containers either individually or as a plurality of groups of first containers sharing a common second container, the second containers being further adapted to contain a fluid in such a way that it can pass into the first containers through the porous plugs; and a plurality of third containers grouped together and corresponding in number to the first containers.

Viewed from yet another aspect the invention provides apparatus for solid-phase synthesis comprising:

a plurality of reaction tubes, each reaction tube being provided at its lower end with a porous filter, the reaction tubes being joined into a plurality of groups, each group comprising a plurality of tubes; and

a reaction block having formed therein a plurality of reaction wells, each reaction well being dimensioned to receive one of said groups of reaction tubes.

It will be seen from the above description that the present invention allows a solid substrate to be deposited in a first container at the start of a solid-phase synthesis reaction, which substrate need only be removed from that container when the reaction is complete and the product has been cleaved from the substrate. Thus, the substrate may be deposited robotically in the first container and the first container may then be accurately handled by a robot during the rest of the process, such that the substrate does not need to be handled directly.

Some embodiments of the invention will now be described by way of example only and with reference to the accompanying drawings, in which:

Figure 1 is a view of a reaction tray and a number of tubes in accordance with the invention;

Figure 2 is a view of a block in accordance with the invention;

Figure 3 is a view of a filtration tray and tubes in accordance with the present invention;

Figure 4 is a view of a block in accordance with an alternative embodiment of the invention;

Figure 5 is a detailed view of an insert of the embodiment of Figure 4;

Figure 6 is a schematic plan view of a robotically operated washing system according to the invention;

Figure 7 shows an alternative tube design according to the invention; and

Figure 8 shows a sectional view of the tube design of Figure 7.

Figure 1 shows a support tray 2 which supports a plurality of molded thermoplastic tubes 4. The support tray 2 is a convenient means for holding the tubes 4 in an organised array. The support tray 2 is shown as comprising an array of 4 by 6 wells 6 for clarity although a more standard size for such trays is 8 by 12 wells. Of course, the exact arrangement of the wells is not vital to the invention.

The tubes 4 are cylindrical in shape, open at both ends and have a lower recessed portion 8 which push fits into the mouth of the wells 6 of the support tray 2. Located in the lower opening of each tube 4, in the region of the recessed portion 8 is a disc of nylon frit 10. The nylon frit 10 acts as a porous base for the tube 4. The tubes 4 are connected together to form a unit corresponding to one column of the support tray 2.

The tubes 4 are push fit into the wells 6 of the support tray 2 and a measured amount of resin 12 having a compound A chemically bonded thereto is transferred as a slurry into each of the tubes 4 by a robot (not shown). In figure 1 only 8 tubes 4 are shown for the sake of simplicity. However, in practice each of the wells 6 of the support tray 2 would be fitted with a tube 4.

Figure 2 shows a block 14 of PTFE having a

plurality of elongate holes 16 formed therein. Each of the holes 16 contains a solution of compound B. The tubes 4 are positioned in the holes 16 so that the solution permeates through the frit 10 and the compound A bonded to the resin 12 can react with compound B to form a product C which is also chemically bonded to the resin 12. The volume of solution in each hole 16 is sufficient that an air gap will be left between the surface of the solution and the upper surface of the block 14 when the tubes 4 are positioned in the holes 16. A lid (not shown) is positioned on the upper surface of the block 14 once all the holes 16 contain tubes 4 and is fixed in position by screws (not shown). A rubber seal (not shown) is interposed between the lid and the upper surface of the block 14 to seal the block. The seal corresponds in shape to the upper surface of the block 14 with corresponding cut-outs for the holes 16.

The sealed block is then placed on an orbital shaker and agitated to allow the reaction to take place between compounds A and B. Once the reaction is deemed to have taken place, the lid is removed from the block 14 and the tubes 4 are removed from the block 14.

As shown in Figure 3, the tubes 4 are located in wells 18 of a filtration tray 20. Each well of the filtration tray is formed at its lower end into a frusto-conical funnel 22. The filtration tray 20 is located on a collection tray 24 such that abutment between the upper perimeter of the collection tray 24 and the lower perimeter of the filtration tray 20 locates each of the funnels 22 in a respective well 26 of the collection tray 24, with the outer faces of funnels 22 spaced from the inner faces of the wells 26.

The resin 12 in each tube 4 is washed through with a suitable washing solution and then with a cleaving solution which cleaves the product C from the resin 12. The product C is then collected in each of the wells 26

of the collection tray 24 and concentrated.

Figure 4 shows an alternative embodiment of the present invention in which the tubes 4 are provided with a PTFE insert 30. The insert 30 is shaped to fit into the holes 16 of the block 15 and is itself provided with recessed channels 32 which pass transversely through the block. The channels 32 are recessed at their upper end to receive, as a push fit, the recessed portions 8 of the tubes 4, as shown in Figure 5. The inserts 30 are positioned in the bottom of each of the holes 16 of the block 14 and when the tubes 4 are positioned in the holes 16, the frit 10 of each tube 4 is maintained in position by the bottom edge of the recesses of the channels 30. Nevertheless, the solution of compound B may still pass through the frit 10. The inserts 30 hold the tubes 4 proud of the upper surface of the block 14, such that the tubes may be easily removed from the block by a robot. Consequently, the lid (not shown) of the block is provided with recesses to accommodate the projecting ends of the tubes 4.

The insert 30 also provides support at other stages of the reaction process. For example, the insert 30 may be used to support the tubes 4 when the resin 12 is deposited therein, thereby obviating the need for the support tray 2. Furthermore, when the resin 12 is washed to remove excess reagent before cleaving, the insert 30 may be used to support the tubes 4, thereby obviating the need for the filtration tray 30 at this stage.

It has been found that, in some cases, the washing stage of the synthesis process is both time consuming and repetitive. Thus, according to a further development of the invention, there is shown in Figure 6 an arrangement for the automatic washing of the resin 12 in each tube 4 after the product C has been formed thereon.

Referring to Figure 6, a platform is shown on which

is mounted a plurality, (four in the example shown) of bases 34 which each removably locate at least one block 14 in a predefined location and orientation on the platform. The bases 34 are formed of any suitable material, such as PTFE. The platform also mounts a robot 36, such as a Toshiba SR-654HSP robot, at a fixed location relative to the bases 34. The robot 36 is of the type having a gripping mechanism (not shown) on an arm (also not shown) which can be orientated in all three degrees of freedom and can be positioned at any point in three-dimensions within its operating range. The robot 36 operates under the control of a robot controller 38 via electrical connections 40. The controller 38 is provided with an input unit 42 for editing the commands of the program running in the controller 38. The robot controller 38 is also connected to a system controller 44 via a link 46. The system controller 44 controls the operation of the other components of the automated washing system, via the electrical connections shown in dotted lines, under the direction of the program running in the robot controller 38. The components controlled by the system controller 44 are: a sonic bath 46 which can be turned on and off for washing the resin 12 in the tubes 4; a multiple (in the example, 8-way, Hamilton MVP(8)) valve 48 for selecting the solvents to be used for washing the resin 12 from the solvent supplies 50; a pump 52 (Hamilton PSD/2 syringe pump in this example) for supplying the solvents to the valve 48; and a vacuum pump 54.

A wash block 56 is provided on a base 34a which locates it removably at a fixed location relative to the robot 36. The wash block 56 is made of a suitable material, such as PTFE, and has formed therein a channel 58 dimensioned to receive one or more tubes 4. The channel has a narrowed portion at its bottom defined by two opposed, longitudinal inwardly directed steps, each having a flat upper surface. The tubes 4, when fitted

to an insert 30, as shown in Figures 4 and 5 are supported on the upper surfaces of the steps in the wash block 56. When in the wash block 56, the lower surface of the insert 30 locates relative to the upper surfaces of the steps and the outer vertical faces of the insert 30 locate relative to the inner vertical faces of the channel 58 sufficiently closely that a semi-sealing effect is achieved. Thus, when the vacuum pump 54, which is connected via a cold trap 60, a waste collection container 62 and a fluid line 64 to the narrowed portion of the wash block 56, is activated it is able to suck any fluid (e.g. solvent or reagent) out of the tubes 4 in the wash block, due to the semi sealing effect described above.

The operation of the automatic washing system will now be described. A reaction block 14b is positioned on the base 34 and contains a plurality of tubes 4 containing the resin 12 to which is bonded the product C. This block 14b may also still contain the reagent B within the holes 16. Each of the tubes 4 is mounted in an insert 30 within the holes 16 of the block 14b. Adjacent the block 14b in the base 34 is positioned a clean block 14a into which the tubes 4 will be deposited once the resin 12 has been washed. The clean block 14a is positioned on the side of the block 14b furthest from the path of the arm of the robot 36 so that the tubes 4 from block 14b do not have to pass over the clean block 14a until they have been washed, thereby preventing contamination of the clean block 14a.

Firstly, the robot arm moves to the block 14b and positions itself over the first hole 16. The gripping mechanism then grips the protruding ends of the tubes 4 in the first hole 16 and lifts the tubes 4, together with the associated insert 30, out of the hole 16. The arm holds the tubes 4 a short distance above the hole 16 to allow any excess fluid to drain through the frit 10 of each tube 4 back into the hole 16.

After a short delay to allow for draining, the arm moves the tubes over to and releases them into the sonic bath 46. The system controller 44 then activates the sonic bath 46 for a predetermined period to wash the resin 12. In the sonic bath 46 the tubes 4 are held in a fixed location while washing solution circulates around them and they are subjected to vibration at sonic frequencies.

After the sonic washing, the system controller 44 deactivates the sonic bath 46 and the robot arm grips the tubes 4 and lifts them from the sonic bath 46. The tubes 4 are held over the sonic bath 46 for a short period to allow any excess washing fluid to drain from them. The vacuum pump 54 is then activated by the system controller 44 and the tubes 4 are placed by the robot arm in the channel 58 of the wash block 56, which is located on base 34a. The vacuum pump 54 draws fluid from the tubes 4 into waste container 62 via fluid line 64. The robot arm then grips the wash block 56 and locates it under the outlets 66 of the valve 48. A respective solvent outlet 66 is provided corresponding to each tube 4 in the wash block 56 and by control of the valve 48 and pump 52 a variety of washing sequences using any of the solvents 50 can be carried out, with excess solvent being removed by the vacuum pump 54 to the waste container 62.

Once the desired washing sequence has been carried out, the vacuum pump 54 is deactivated by the system controller 44, after a period long enough for any remaining solvent to be drawn off, and the wash block 56 is returned to the base 34a by the robot arm. The tubes 4 are then removed from the wash block 56 by the robot arm and placed in a hole 16 of the clean block 14a corresponding to the hole 16 in which they started in the block 14b.

The above process is repeated for each set of tubes in each hole 16 in block 14b and then for each block 14b

on each base 34.

If desired, the platform described above may be operated under an enclosure from which a build-up of atmosphere may be removed.

As a particular refinement of the above system, the inner edges of the holes 16 of the blocks 14, the lower edges of the insert 30 and the upper edges of the channel 58 of the wash block 56 are chamfered to allow greater tolerance in the positioning of the components by the robot 36.

Figures 7 and 8 show an alternative design of tubes 4a. In this design, the tubes 4a are held to their neighbouring tubes by a plurality (four, as shown) of bridging members 5a which can be easily broken by deformation in order to separate the tubes 4a for individual processing. The tubes 4a have a frusto-conical recessed portion 8a for easy location in the insert 30 and each recessed portion is provided with an internal lip 9a for retaining the nylon frit 10.

Claims

1. A method for solid phase synthesis, wherein there is provided a first container having deposited therein a permeable, solid phase substrate to which is bonded a first reagent, the first container having a porous base; the first container is placed in a second container; a solution of a second reagent in the second container is permitted to permeate through the porous base of the first container; the second reagent is allowed to react with the first reagent to produce a product bonded to the substrate; the first container is removed from the second container; and a cleaving solution is washed through the first container to cleave the product from the resin, the cleaving solution and the cleaved product being collected in a third container.

2. A method as claimed in claim 1, wherein said first container is tubular.

3. A method as claimed in claim 2, wherein said first container has openings at both ends and is provided with a porous plug at one end.

4. A method as claimed in claim 3, wherein said porous plug is frictionally retained in said first container.

5. A method as claimed in any preceding claim, wherein there are provided a plurality of said first containers.

6. A method as claimed in claim 5, wherein said first containers are arranged into at least one connected group.

7. A method as claimed in claim 6, wherein said second container is adapted to receive said group of first containers.

8. A method as claimed in any preceding claim, wherein there are provided a plurality of said second containers grouped together.

9. Apparatus for carrying out solid phase synthesis comprising a plurality of first containers which are tubular, have openings at either end and are provided with a porous plug at one end; a plurality of second containers grouped together and adapted to receive the first containers either individually or as a plurality of groups of first containers sharing a common second container, the second containers being further adapted to contain a fluid in such a way that it can pass into the first containers through the porous plugs; and a plurality of third containers grouped together and corresponding in number to the first containers.

10. Apparatus as claimed in claim 9, wherein means are provided for removing said first container from said second container, comprising a protrusion which friction fits in an upper opening of said first container.

11. A method for solid phase synthesis comprising the steps of:

providing a plurality of reaction tubes, each reaction tube being provided at its lower end with a porous filter, and containing a solid-phase substrate having a first reagent bonded to a surface therefore, the reaction tubes being joined into a plurality of groups, each group comprising a plurality of tubes;

providing a reaction block having formed therein a plurality of reaction wells, each dimensioned to receive one of said groups of reaction tubes and each containing a second reagent in fluid form; and

locating the groups of reaction tubes in respective reaction wells such that the second reagent permeates through the porous filter of each reaction tube and

reacts with the first reagent bonded to the solid-phase substrate in each reaction tube to form a product bonded to the solid-phase substrate.

12. Apparatus for solid-phase synthesis comprising:

a plurality of reaction tubes, each reaction tube being provided at its lower end with a porous filter, the reaction tubes being joined into a plurality of groups, each group comprising a plurality of tubes; and

a reaction block having formed therein a plurality of reaction wells, each reaction well being dimensioned to receive one of said groups of reaction tubes.

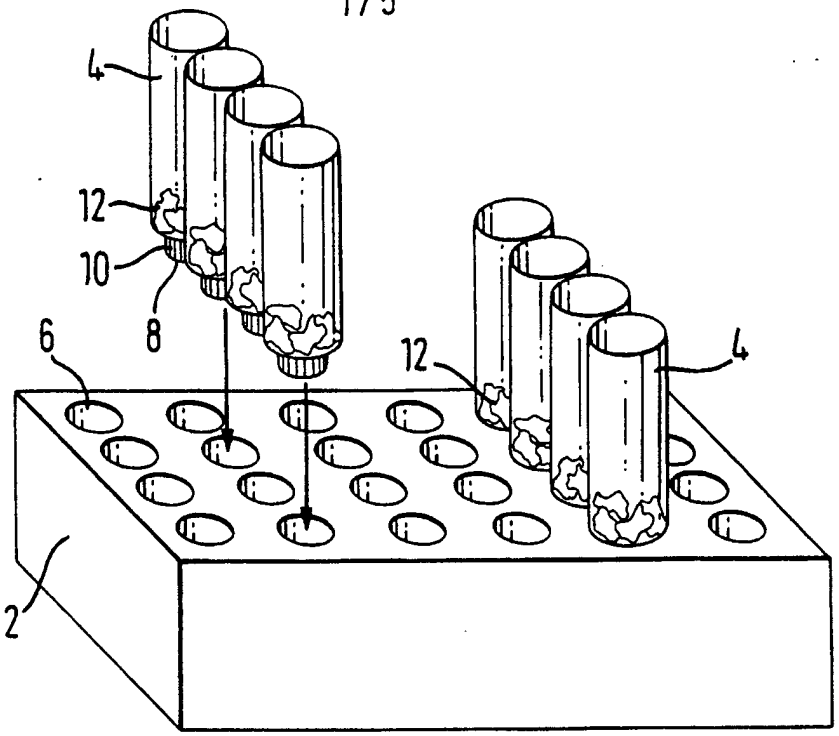

FIG. 1

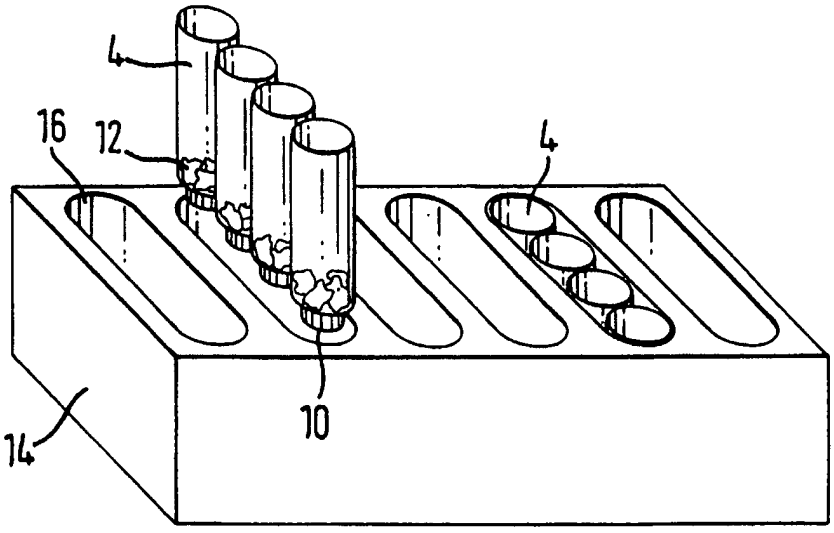

FIG. 2

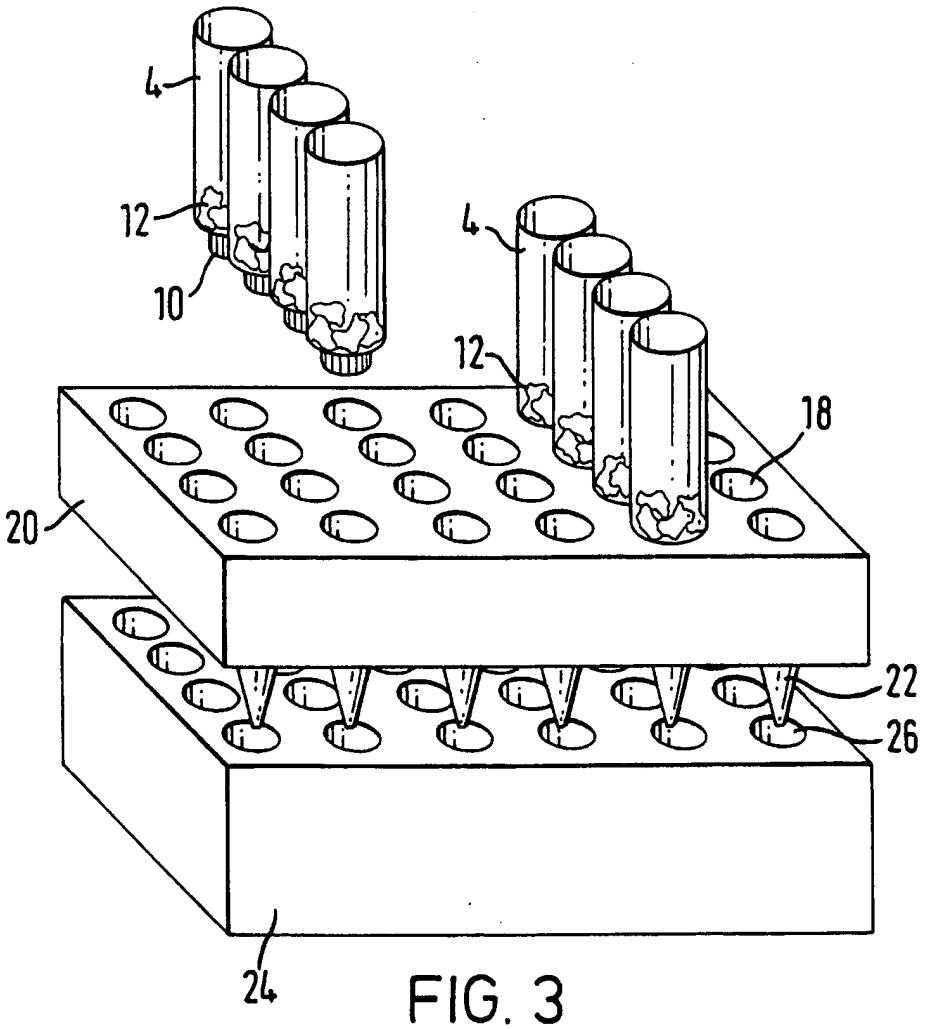

FIG. 3

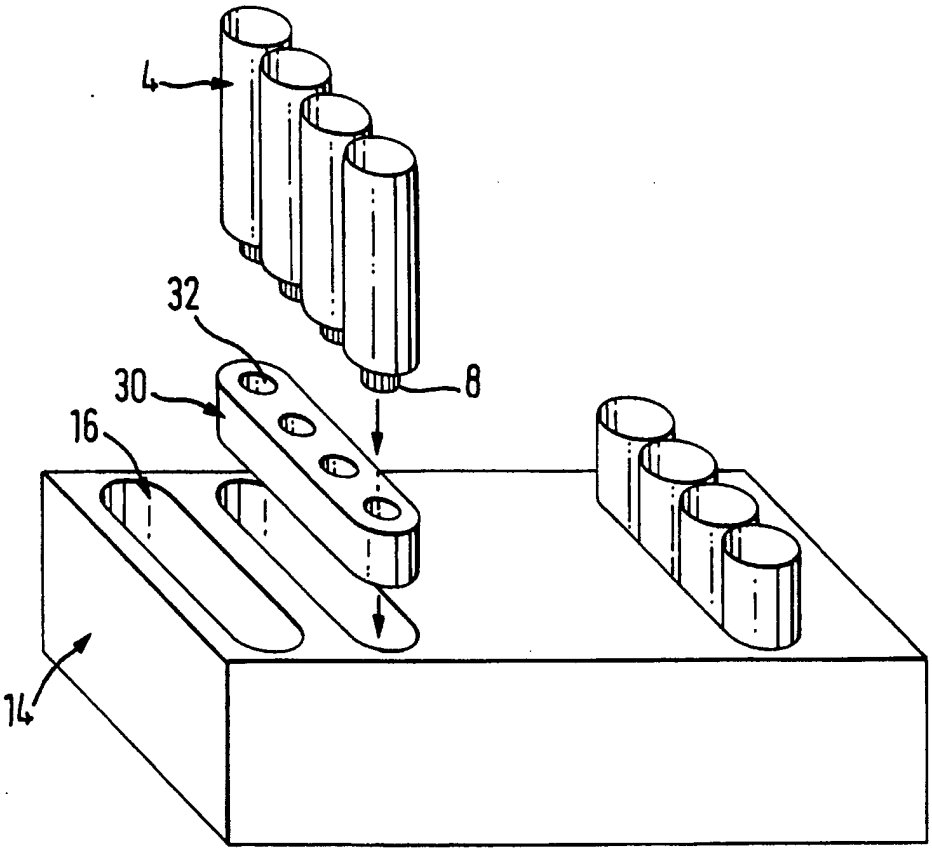

FIG. 4

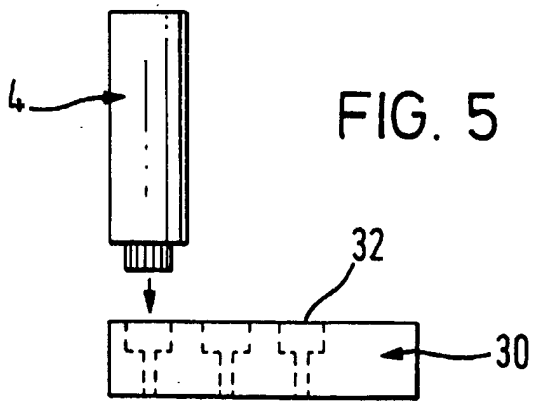

FIG. 5

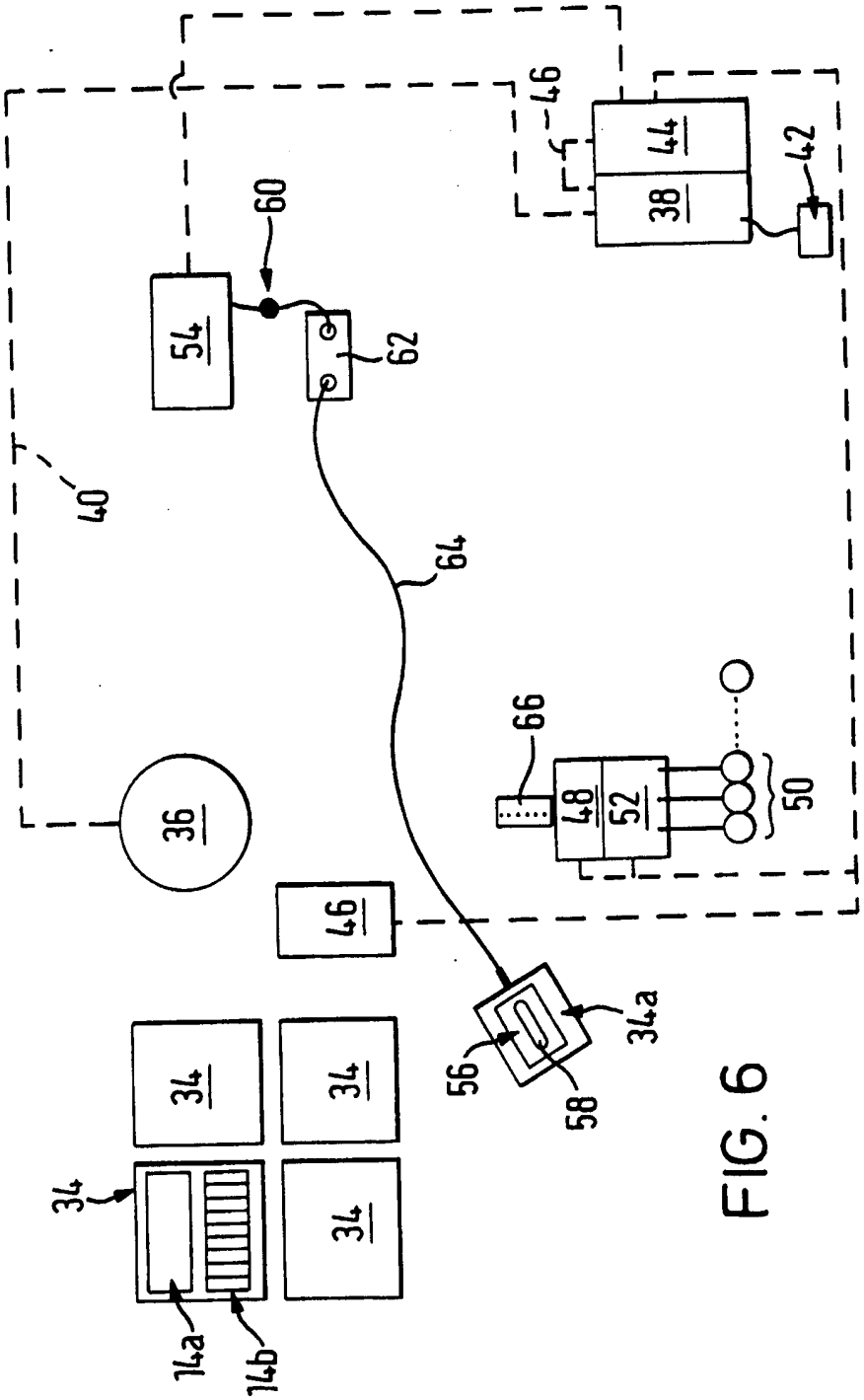
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FIG. 6

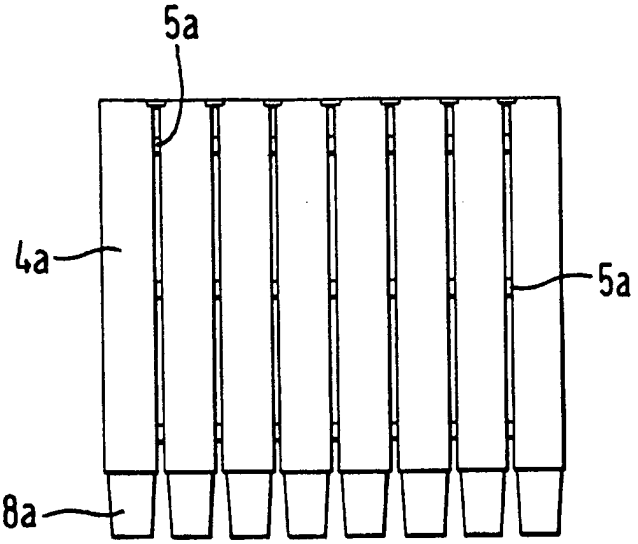

FIG. 7

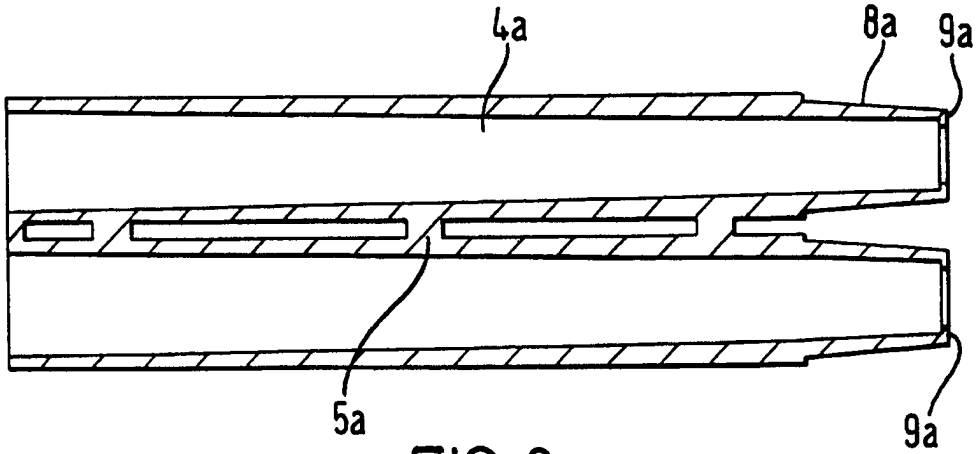

FIG. 8

INTERNATIONAL SEARCH REPORT

Ir ıtional Application No
PCT/GB 98/00596

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 B01J19/00

According to International Patent Classification(IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 B01J

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 94 08711 A (WARNER-LAMBERT COMPANY) 28 April 1994 see abstract see page 14, line 3 - page 16, line 23 see page 25, line 3 - page 28, line 11 see figures	1-3,5-9, 11,12
A	see page 6, line 15 - page 8, line 18	4,10
A	DE 37 23 004 A (BOEHRINGER INGELHEIM KG) 26 January 1989 see the whole document	1-12
A	US 5 437 979 A (JANG B. RAMPAL & JON F. HARBAUGH) 1 August 1995 see the whole document	1-12

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
5 June 1998	16/06/1998

Name and mailing address of the ISA	Authorized officer
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INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 98/00596

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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A	H.GAUSEPOHL ET AL.: "A multiple reaction system for automated simultaneous peptide synthesis" 1991 , ESCOM , LEIDEN, NL XP000353588 190790 PEPTIDES 1990, PROCEEDINGS OF THE 21ST EUROPEAN PEPTIDE SYMPOSIUM, SEPTEMBER 2-8, 1990, PLATJA D'ORO, SPAIN, ED. E. GIRALT & D. ANDREU see page 206 - page 207	1-12
A	EP 0 514 927 A (WALTER GILBERT) 25 November 1992 see abstract see page 13, line 4 - line 16 see figure 13	

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INTERNATIONAL SEARCH REPORT

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